European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 86 30 3158

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl 4)
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 105, no. 23, 16th November 1983, pages 6915-6922, American Chemical Society; C.M. HARRIS et al.: "Vancomycin: Structure and transformation to CDP-I" * Page 6915, column 1, lines 44-50; page 6917, column 2, lines 2-3 *	1,7	C 07 K 9/00 A 61 K 37/02
A	EP-A-0 112 184 (ELI LILLY) * Page 3, lines 4-6; pages 29-34; claim 1 *	1,7	
P,A	EP-A-0 159 180 (ELI LILLY) * Pages 15-18; claim 1 *	1,7	

TECHNICAL FIELDS SEARCHED (Int. Cl 4)

C 07 K 9/00
A 61 K 37/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23-09-1987	BRENNAN J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03.82

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 201 251**
A3

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **86303158.9**

(51) Int. Cl.⁴: **C07K 9/00** , A61K 37/02

(22) Date of filing: **25.04.86**

(30) Priority: **25.04.85 US 726731**

(43) Date of publication of application:
17.12.86 Bulletin 86/46

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(88) Date of deferred publication of the search report:
16.12.87 Bulletin 87/51

(71) Applicant: **ELI LILLY AND COMPANY**
Lilly Corporate Center
Indianapolis Indiana 46285(US)

(72) Inventor: **Nagarajan, Ramakrishnan**
5 West 79th Street
Indianapolis Indiana 46260(US)
Inventor: **Schabel, Amelia Apolinaria**
4455 Broadway
Indianapolis Indiana 46205(US)

(74) Representative: **Tapping, Kenneth George et al**
Erl Wood Manor
Windlesham Surrey, GU20 6PH(GB)

(54) **Novel glycopeptide derivatives.**

(57) Novel glycopeptide antibiotics can be prepared from the glycopeptide antibiotics vancomycin, A51568A, A51568B, M43A and M43D by reaction with a ketone or aldehyde followed, if appropriate, by reduction.

EP 0 201 251 A3

comycin; N^{van}-(p butyloxybenzyl)vancmoycin; N^{van}-(n-decyl)vancomycin; N^{van}-(p -octylbenzyl)-vancomycin; or N^{van}-(p-octyloxybenzyl)vancomycin.

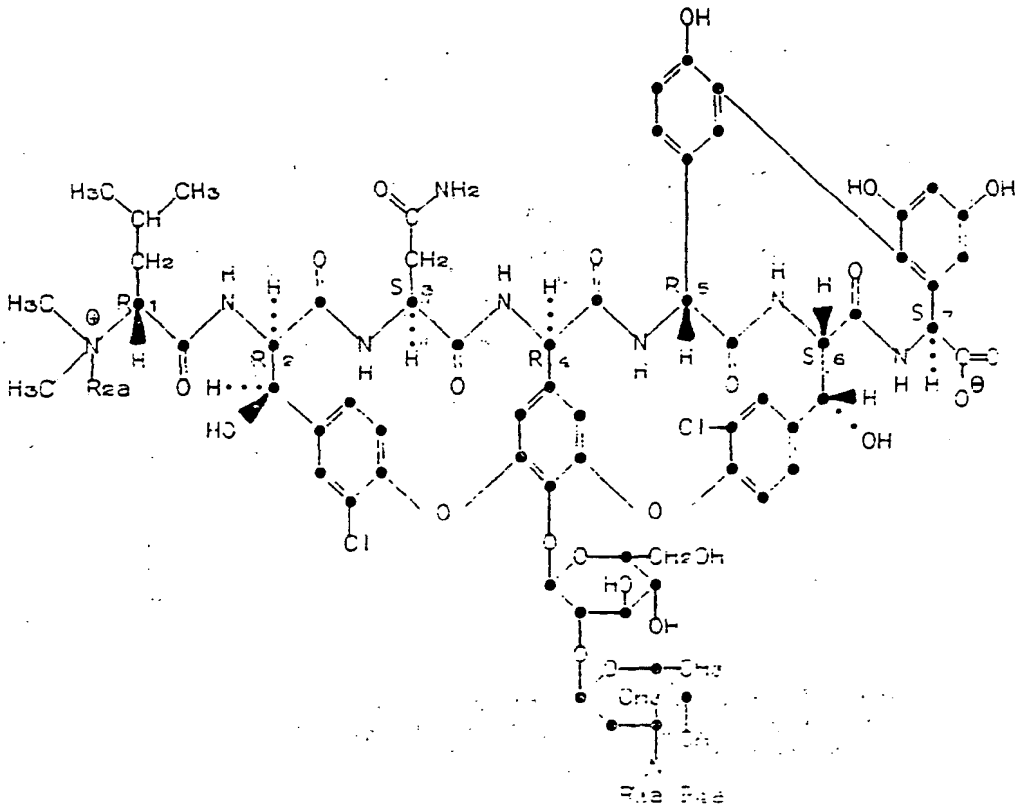
R_1 and R_2 or R_3 and R_4 together form an R_5-(C_1-C_6 alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group;

R_5 is C_1-C_{10}-alklyl, C_2-C_{10}-alkenyl, C_3-C_{10}-cycloalkyl, C_5-C_{12}-cycloalkenyl, phenyl, napththyl, indenyl, tetralinyl, decalinyl, adamantyl, a monocyclic heterocyclic ring system comprising 3 to 8 atoms in the ring or a bicyclic heterocyclic ring system comprising 6 to 11 atoms, provided that at least one atom of the ring system is carbon and at least one atom of the ring system is a heteroatom selected from O,N and S, and wherein R_5 may be substituted with one or more hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkylthio, halo or amino groups; and

n = 1 or 2;

provided that: 1) at least one of R_2 and R_3 must be other than hydrogen; and 2) when n is 2, R must be hydrogen.

3. A process as claimed in claim 1 for preparing a compound having the structure 2:



2

wherein R_{2a} is hydrogen or methyl;

R_{3a} is R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl);

and

R_{4a} is hydrogen; or

R_{3a} and R_{4a} together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group and salts thereof.

4. A process as claimed in claim 1 or 2, wherein R_7 is a group of formula R_6R_7CH-and R_3 is hydrogen.

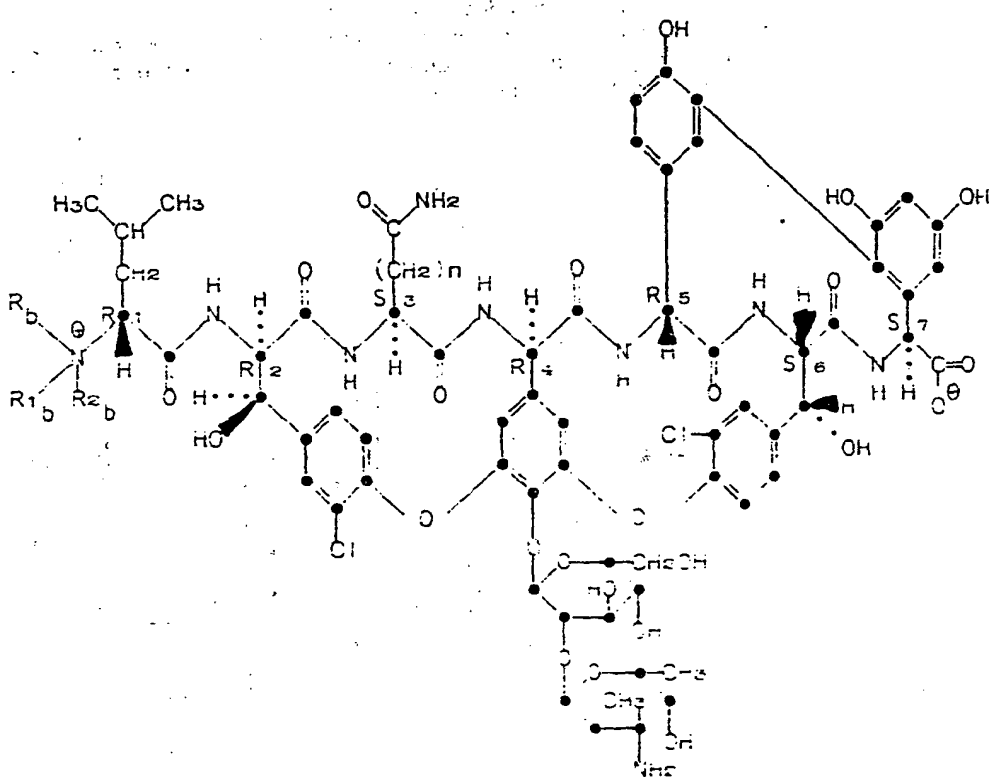
5. A process as claimed in claim 1 for preparing N^{van}-(benzyl)vancomycin; N^{van} -(p-butylbenzyl)-van-

wherein R_4 and R_7 are R_5, R_5-(C_1-C_5 alkyl) or R_5-(C_2-C_5-alkenyl);

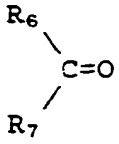
and n is 1 or 2;

provided that: 1) at least one of R_2 and R_3 must be other than hydrogen; 2) when n is 2, R must be hydrogen; 3) when R is methyl and R_3 is hydrogen, R_2 cannot be methyl and 4) when R and R_1 are both methyl, then R_2 is hydrogen or methyl and n is 1;

or a pharmaceutically-acceptable salt thereof; which comprises reacting a compound of formula



wherein R_b, R_{1b} and R_{2b} independently represent hydrogen or methyl, and n is 1 or 2, with a ketone or aldehyde of formula:



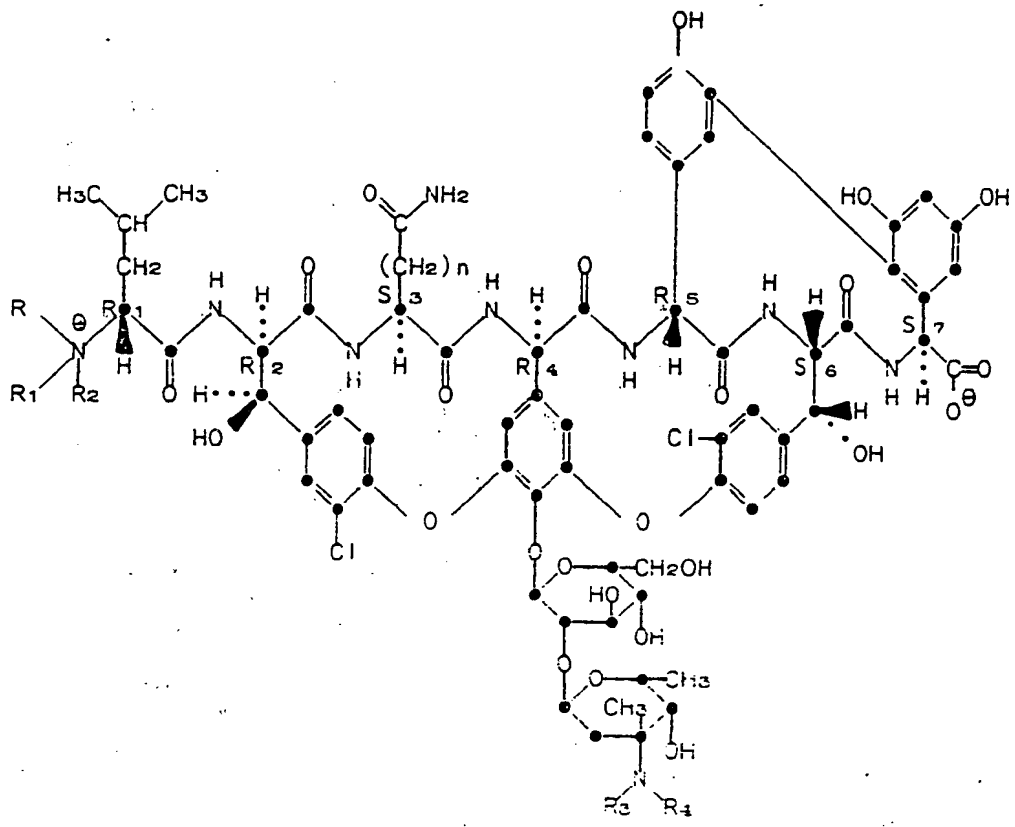
so as to form an alkylidene or alkenylidene derivative, optionally followed by reduction so as to form an alkyl or alkenyl derivative.

2. A process according to claim 1, wherein R is hydrogen or methyl;

R_6 is hydrogen;

R_2 and R_3, independently, are hydrogen, R_5-(C_1-C_5)-alkyl or R_5-(C_2-C_5-alkenyl); and

R_4 is hydrogen; or



1

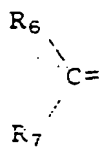
wherein R and R_1 are independently hydrogen or methyl;

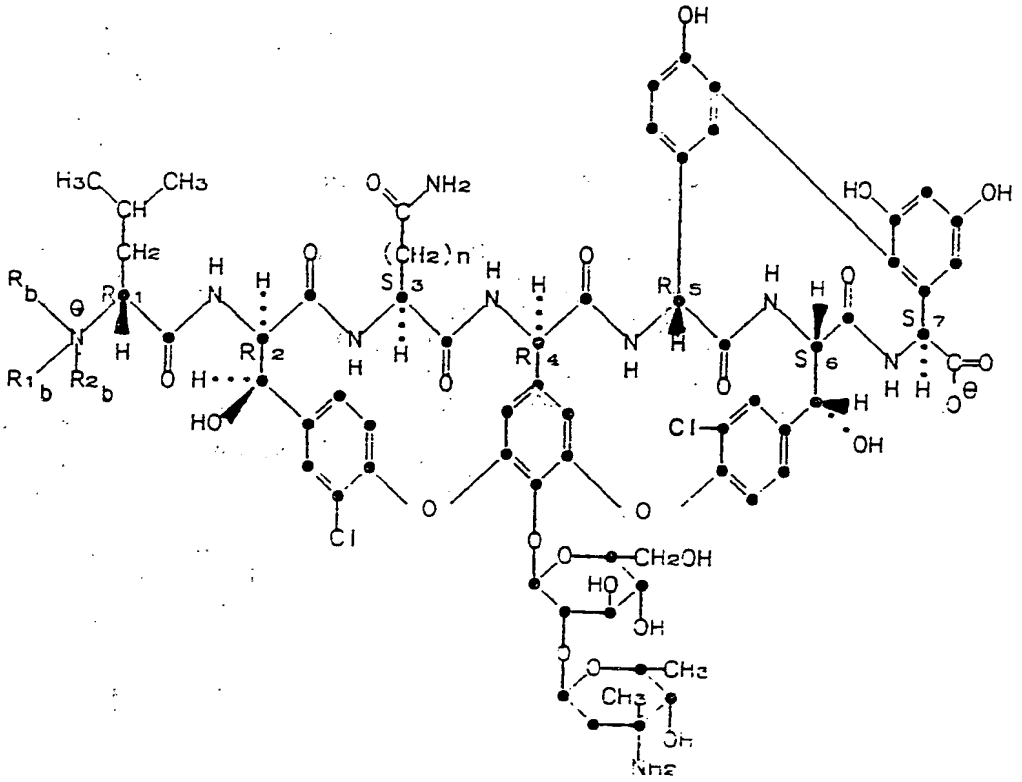
R_2 and R_3, independently, are hydrogen, or a group of formula: R_6R_7CH-where R_6 and R_7 are independently R_5, R_5-(C_1-C_5)-alkyl or R_5-(C_2-C_5-alkenyl)

wherein R_5 is hydrogen, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_1-C_4 alkoxy, C_3-C_{10}-cycloalkyl, C_5-C_{12}-cycloalkenyl, phenyl, napththyl, indenyl, tetralinyl, decalinyl, adamantyl, a monocyclic heterocyclic ring system comprising 3 to 8 atoms in the ring or a bicyclic heterocyclic ring system comprising 6 to 11 atoms, provided that at least one atom of the ring system is carbon and at least one atom of the ring system is a heteroatom selected from O,N and S, and wherein R_5 may be substituted with one or more hydroxy, nitro, C_1-C_{10}-alkoxy, C_1-C_{10} alkyl, phenyl, C_1-C_6-alkylthio, nitrile, halo, C_2-C_4 acylamino, amino, C_1-C_4 dialkylamino groups; and

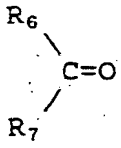
R_4 is hydrogen; or

R_1 and R_2 and/or R_3 and R_4 together form a group of the formula





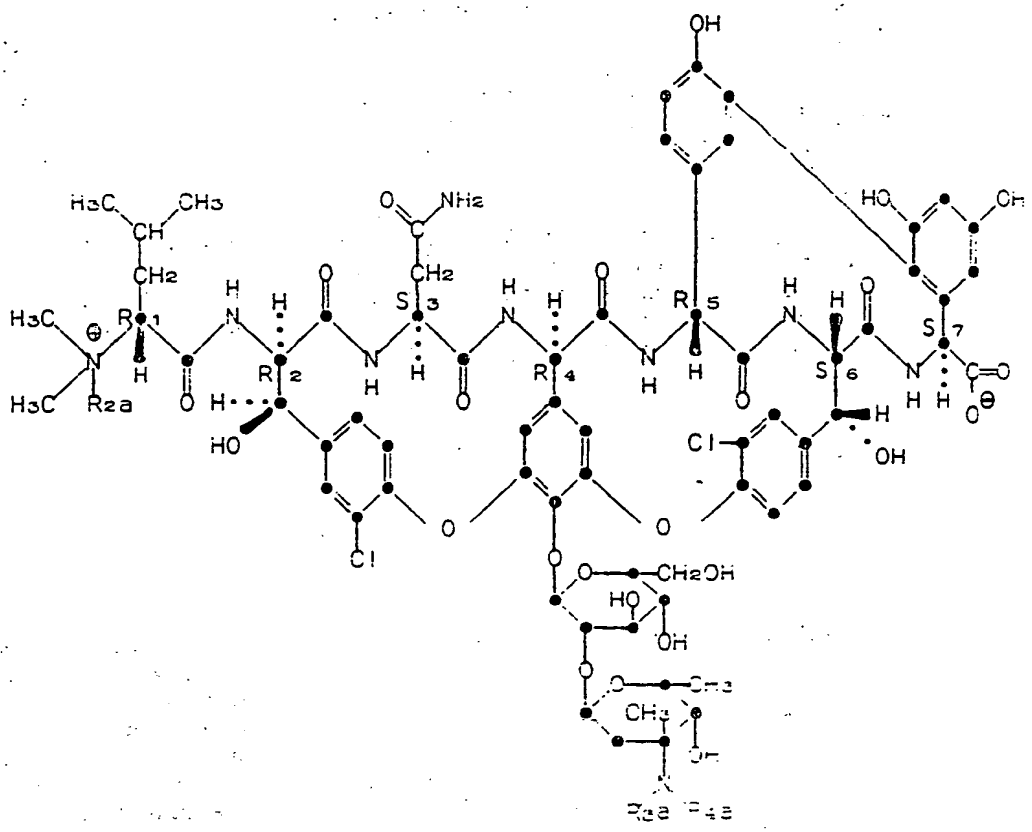
wherein R_b, R_{1b} and R_{2b} independently represent hydrogen or methyl, and n is 1 or 2, with a ketone or aldehyde of formula:



so as to form an alkylidene or alkenylidene derivative, optionally followed by reduction so as to form an alkyl or alkenyl derivative.

CLAIMS FOR CONTRACTING STATE : AT

1. A process for preparing a compound of formula (I):



2

wherein R_{2a} is hydrogen or methyl;

R_{3a} is R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl);

and

R_{4a} is hydrogen; or

R_{3a} and R_{4a} together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group and salts thereof.

4. A compound as claimed in claim 1 or 2, wherein R_2 is a group of formula R_6R_7CH-and R_3 is hydrogen.

5. A compound as claimed in claim 1 which is N^{van}-(benzyl)vancomycin; N^{van}-(p-butyloxybenzyl)-vancomycin; N^{van}-(p-butyloxybenzyl)vancomycin; N^{van}-(n-decyl)vancomycin; N^{van}-(p-octylbenzyl)-vancomycin; or N^{van}-(p-octyloxybenzyl)vancomycin.

6. A pharmaceutical formulation comprising as an active ingredient a compound as claimed in any one of claims 1 to 5, associated with a pharmaceutically-acceptable carrier therefor.

7. A compound as claimed in any one of claims 1 to 5 for use as an antibacterial.

8. A process for preparing a compound as claimed in any one of claims 1 to 5, which comprises reacting a compound of formula

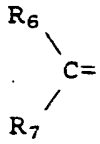
wherein R and R_1 are independently hydrogen or methyl;

R_2 and R_3, independently, are hydrogen, or a group of formula: R_6R_7CH-, where R_6 and R_7 are independently R_5, R_5-(C_1-C_5)-alkyl or R_5-(C_2-C_5-alkenyl)

wherein R_5 is hydrogen, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_1-C_4-alkoxy, C_3-C_{10}-cycloalkyl, C_5-C_{12}-cycloalkenyl, phenyl, napththyl, indenyl, tetralinyl, decalinyl, adamantyl, a monocyclic heterocyclic ring system comprising 3 to 8 atoms in the ring or a bicyclic heterocyclic ring system comprising 6 to 11 atoms, provided that at least one atom of the ring system is carbon and at least one atom of the ring system is a heteroatom selected from O,N and S, and wherein R_5 may be substituted with one or more hydroxy, nitro, C_1-C_{10}-alkoxy, C_1-C_{10} alkyl, phenyl, C_1-C_6-alkylthio, nitrile, halo, C_2-C_4 acylamino, amino, C_1-C_4 dialkylamino groups; and

R_4 is hydrogen; or

R_1 and R_2 and/or R_3 and R_4 together form a group of the formula



wherein R_6 and R_7 are R_5, R_5-(C_1-C_5 alkyl) or R_5-(C_2-C_5-alkenyl);

and n is 1 or 2;

provided that: 1) at least one of R_2 and R_3 must be other than hydrogen; 2) when n is 2, R must be hydrogen; 3) when R is methyl and R_3 is hydrogen, R_2 cannot be methyl and 4) when R and R_1 are both methyl, then R_2 is hydrogen or methyl and n is 1;

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R is hydrogen or methyl;

R_1 is hydrogen;

R_2 and R_3, independently, are hydrogen, R_5-(C_1-C_6)-alkyl or R_5-(C_2-C_6-alkenyl); and R_4 is hydrogen; or

R_1 and R_2 or R_3 and R_4 together form an R_5-(C_1-C_6 alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group;

R_5 is C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_3-C_{10}-cycloalkyl, C_5-C_{12}-cycloalkenyl, phenyl, napththyl, indenyl, tetralinyl, decalinyl, adamantyl, a monocyclic heterocyclic ring system comprising 3 to 8 atoms in the ring or a bicyclic heterocyclic ring system comprising 6 to 11 atoms, provided that at least one atom of the ring system is carbon and at least one atom of the ring system is a heteroatom selected from O,N and S, and wherein R_5 may be substituted with one or more hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkylthio, halo or amino groups;

and

n = 1 or 2;

provided that: 1) at least one of R_2 and R_3 must be other than hydrogen; and 2) when n is 2, R must be hydrogen;

or pharmaceutically-acceptable salt thereof.

3. A compound as claimed in claim 1 having the structure 2:

N^{van}-(p-octyloxybenzyl)vancomycin, M^+ + 1 = 1665

N^{van} -(p-methoxybenzyl)vancomycin, M^+ + 1 = 1568

N^{leu}-(6-nitro-3,4-dimethoxybenzyl)vancomycin, M^+ + 1 = 1642

N^{leu}-(6-nitro-3,4-dimethoxybenzyl)vancomycin, M^+ + 1 = 1642

N^{leu}-(p-methoxybenzyl)vancomycin (65% pure), M^+ + 1 = 1568

N^{van},N^{leu}-(p-methoxybenzyl)vancomycin, M^+ + 1 = 1668

N^{van} -(n-bromobenzyl)vancomycin, M^+ = 1617

N^{van}-(o-bromobenzyl)vancomycin, M^+ = 1617

N^{van}-(p-chlorobenzyl)vancomycin, M^+ = 1572

N^{van}-(2,6-dichlorobenzyl)vancomycin, M^+ = 1606

N^{van}-(p-acetamidobenzyl)vancomycin, M^+ = 1595

N^{van}-(phydroxybenzyl)vancomycin, M^+ = 1553

N^{leu}-(p-hydroxybenzyl)vancomycin, M^+ = 1553

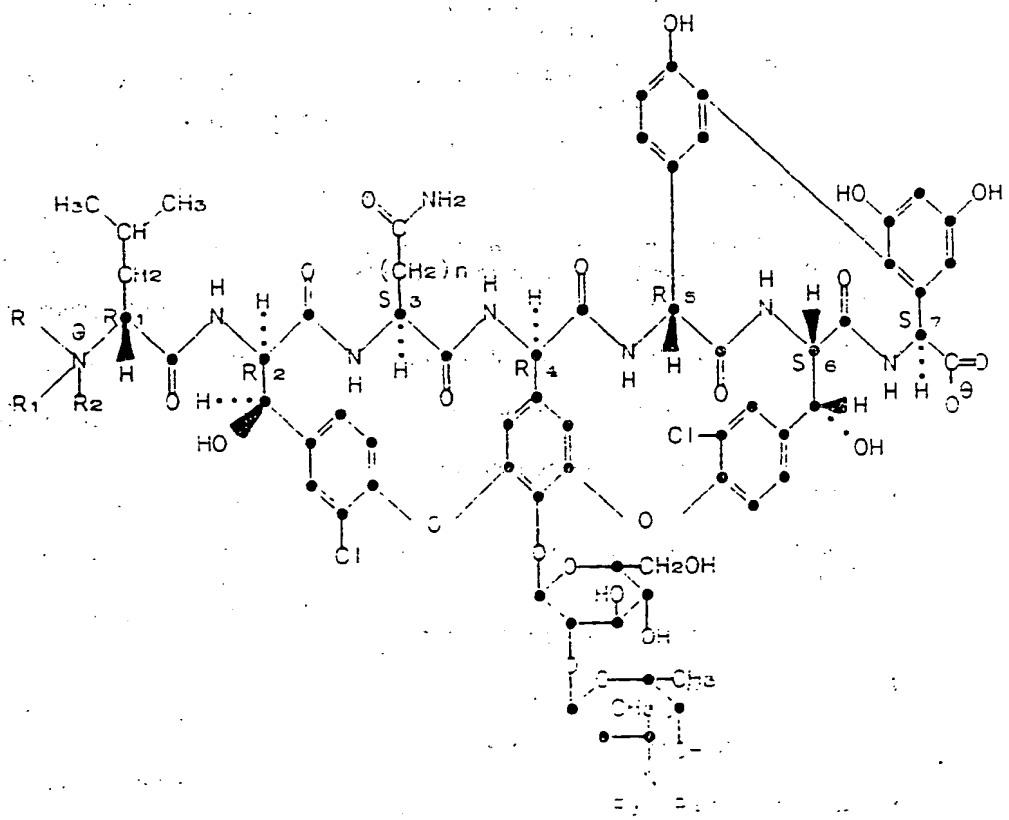
N^{van},N^{leu}-(p-hydroxybenzyl)vancomycin, M^+ = 1659

N^{van}-(p-dimethylaminobenzyl)vancomycin, M^+ + 1 = 1581

N^{van}-(p-cyanobenzyl)vancomycin, M^+ + 1 = 1563

Claims

1. A compound of formula (I):



68 N^{leu}-(3-ethoxy-n-propylidenyl)vancomycin (ni)

37 N^{leu}-(3-ethoxy-n-propyl)vancomycin, $M^+ + 1 = 1534$

90 N^{van}, N^{leu}-di(3-ethoxy-n-propylidenyl)-vancomycin (ni)

38 N^{van}, N^{leu}-di(3-ethoxy-n-propyl)-vancomycin, $M^+ + 1 = 1619$

111 N^{van}-(5-hydroxy-n-pentylidenyl)-vancomycin (ni)

31 N^{van}-(5-hydroxy-n-pentyl)vancomycin, $M^+ = 1533$

66 N^{leu}-(5-hydroxy-n-pentylidenyl)-vancomycin (ni)

32 N^{leu}-(5-hydroxy-n-pentyl)vancomycin, $M^+ = 1533$

88 N^{van}, N^{leu}-di(5-hydroxy-n-pentylidenyl)-vancomycin (ni)

33 N^{van}, N^{leu}-di(5-hydroxy-n-pentyl)-vancomycin, $M^+ = 1619$

123 N^{van}-(3-methylthio-n-propylidenyl)-vancomycin (ni)

53 N^{van}-(3-methylthio-n-propyl)vancomycin, $M^+ = 1536$

77 N^{leu}-(3-methylthio-n-propylidenyl)-vancomycin (ni)

54 N^{leu}-(3-methylthio-n-propyl)vancomycin, $M^+ = 1536$

Similarly prepared were the following reduced compounds. Once again, the intermediate Schiff's bases were not isolated.

N^{van}-(cyclohexylmethyl)vancomycin, $M^+ = 1543$

N^{leu}-(cyclohexylmethyl)vancomycin, $M^+ = 1543$

N^{van}, N^{leu}-di(cyclohexylmethyl)vancomycin, $M^+ = 1639$

N^{van}(p-diethylaminobenzyl)vancomycin, $M^+ + 1 = 1609$

N^{van}(p-isopropylbenzyl)vancomycin, $M^+ = 1579$

N^{van}-(benzyl)vancomycin, $M^+ = 1538$

N^{van}-(p-bromobenzyl)vancomycin, $M^+ = 1617$

N^{van}-(p-butylbenzyl)vancomycin, $M^+ + 1 = 1594$

N^{van}, N^{leu}-(p-butylbenzyl)vancomycin, $M^+ + 1 + 1740$

N^{van}, N^{leu}-(p-butoxybenzyl)vancomycin, $M^+ = 1771$

N^{van}-(p -butoxybenzyl)vancomycin, $M^+ = 1609$

N^{van}-(4-pentylbenzyl)vancomycin, $M^+ + 1 = 1608$

N^{van}-(4-pentyloxybenzyl)vancomycin, $M^+ + 1 = 1624$

N^{van}-(pyrrol-2-ylmethyl)vancomycin, $M^+ 1 = 1526$

N^{van}-(pyridin-2-ylmethyl)vancomycin, $M^+ = 1538$

N^{van}-(furan-2-ylmethyl)vancomycin, (poor spectrum)

N^{van}, N^{leu}-(p-isopropylbenzyl)vancomycin, $M^+ = 1711$

N^{van}-(p-methylthiobenzyl)vancomycin, $M^+ = 1583$

N^{van}, N^{leu}-(p-methylthiobenzyl)vancomycin, $M^+ = 1583$

N^{van}-(p -octylbenzyl)vancomycin $M^+ + 1 = 1650$

Compound	Name
60	N^{leu}-(n-pentylidenyl)vancomycin (ni)
16	N^{leu}-(n-pentyl)vancomycin, $M^+ + 1$=1727
106	N^{van}-(n-butylidenyl)vancomycin (ni)
17	N^{van}-(n-butyl)vancomycin, M^+=1503
83	N^{van}, N^{leu}-di(n-butylidenyl)vancomycin (ni)
19	N^{van}, N^{leu}-di(n-butyl)vancomycin, $M^+ + 1$=1560
61	N^{leu}-(n-butylidenyl)vancomycin (ni)
18	N^{leu}-(n-butyl)vancomycin, M^+=1503
107	N^{van}-(n-propylidenyl)vancomycin (ni)
20	N^{van}-(n-propyl)vancomycin, $M^+ + 1$=1490
84	N^{van}, N^{leu}-di(n-propylidenyl)vancomycin (ni)
22	N^{van}, N^{leu}-di(n-propyl)vancomycin, $M^+ + 1$=1532
62	N^{leu}-(n-propylidenyl)vancomycin (ni)
21	N^{leu}-(n-propyl)vancomycin, $M^+ + 1$=1490
85	N^{van}, N^{leu}-di(ethylidenyl)vancomycin (ni)
24	N^{van}, N^{leu}-diethylvancomycin, M^+=1503
63	N^{leu}-ethylidenylvancomycin (ni)
23	N^{leu}-ethylvancomycin, M^+=1475
28	N^{van}, N^{leu}-dimethylvancomycin (64% pure), M^+=1476
64	N^{leu}-(n-decylidenyl)-A51568A (ni)
25	N^{leu}-(n-decyl)-A51568A, M^+=1573
109	N^{van}-(n-decylidenyl)-A51568A (ni)
26	N^{van}-(n-decyl)-A51568A, M^+=1573
135	N^{van}-(n-decylidenyl)-M43A (ni)
124	N^{van}-(n-decyl)-M43A, $M^+ + 1$=1616
122	N^{van}-(n-undecylidenyl)vancomycin (ni)
52	N^{van}-(n-undecyl)vancomycin, $M^+ + 1$=1602
113	N^{van}-(3-ethoxy-n-propylidenyl)vancomycin (ni)
36	N^{van}-(3-ethoxy-n-propyl)vancomycin, $M^+ + 1$=1534

starting antibiotic, however, the major product is the N^{leu} derivative. Once again the identity of the product was confirmed by fast-atom-bombardment mass spectrometry. The intermediate Schiff's bases were not isolated (ni) but a molecular ion is given in all cases for the reduced alkyl product.

The following compounds were thus prepared:

Compound	Name
99	N^{van}-(n-dodecylidenyl)vancomycin (ni)
1	N^{van}-(n-dodecyl)vancomycin, M^+=1615
79	N^{van}, N^{leu}-di(n-decylidenyl)vancomycin (ni)
4	N^{van}, N^{leu}-di(n-decyl)vancomycin, M^+=1727
55	N^{leu}-(n-decylidenyl)vancomycin (ni)
3	N^{leu}-(n-decyl)vancomycin, $M^+ + 1$=1588
101	N^{van}-(n-nonylidenyl)vancomycin (ni)
5	N^{van}-(n-nonyl)vancomycin, M^+=1573
80	N^{van}, N^{leu}-di(n-nonylidenyl)vancomycin (ni)
6	N^{van}, N^{leu}-di(n-nonyl)vancomycin, M^+=1700
102	N^{van}-(n-octylidenyl)vancomycin (ni)
7	N^{van}-(n-octyl)vancomycin, $M^+ + 1$=1560
81	N^{van}, N^{leu}-di(n-octylidenyl)vancomycin (ni)
9	N^{van}, N^{leu}-di(n-octyl)vancomycin, M^+=1671
57	N^{leu}-(n-octylidenyl)vancomycin (ni)
8	N^{leu}-(n-octyl)vancomycin, $M^+ + 1$=1560
103	N^{van}-(n-heptylidenyl)vancomycin (ni)
10	N^{van}-(n-heptyl)vancomycin, M^+=1545
82	N^{van}, N^{leu}-di(n-heptylidenyl)vancomycin (ni)
12	N^{van}, N^{leu}-di(n-heptyl)vancomycin, $M^+ + 1$=1643
58	N^{leu}-(n-heptylidenyl)vancomycin (ni)
11	N^{leu}-(n-heptyl)vancomycin, M^+=1545
104	N^{van}-(n-hexylidenyl)vancomycin (ni)
13	N^{van}-(n-hexyl)vancomycin, M^+=1531
59	N^{leu}-(n-hexylidenyl)vancomycin (ni)
14	N^{leu}-(n-hexyl)vancomycin, M^+=1531
105	N^{van}-(n-pentylidenyl)vancomycin (ni)
15	N^{van}-(n-pentyl)vancomycin, $M^+ + 1$=1518

Alternatively, the unit dosage form of the antibiotic can be a solution of the antibiotic or preferably a salt thereof in a suitable diluent in sterile, hermetically sealed ampoules. The concentration of the antibiotic in the unit dosage may vary, e.g. from about 1 percent to about 50 percent depending on the particular form of the antibiotic and its solubility and the dose desired by the physician.

In a further aspect, this invention provides a method for treating infectious diseases, especially those caused by Gram-positive microorganisms, in animals. The animal may be either susceptible to, or infected with, the microorganism. The method comprises administering to the animal an amount of a formula (I) compound or its pharmaceutically acceptable salt which is effective for this purpose. In general an effective amount of a formula (I) compound is a dose between about 0.5 and about 100 mg/kg. A preferred dose is from about 10 to about 60 mg/kg of active compound. A typical daily dose for an adult human is from about 250 mg to about 1.0 g.

In practicing this method, the antibiotic can be administered in a single daily dose or in multiple doses per day. The treatment regime may require administration over extended periods of time, e.g., for several days or for from two to three weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms involved in the infection.

A convenient method of practicing the treatment method is to administer the antibiotic via IV infusion. In this procedure a sterile formulation of a suitable soluble salt of the antibiotic is incorporated in a physiological fluid, such as 5% dextrose solution, and the resulting solution is infused slowly IV. Alternatively, the piggy-back method of IV infusion can also be used.

In another embodiment, this invention relates to methods of increasing feed-utilization efficiency in poultry, swine, sheep and cattle, of promoting growth rates in cattle raised for meat production and of enhancing milk production in lactating ruminants. For increasing feed-utilization efficiency and promoting growth, a formula (I) compound is administered orally in a suitable feed in an amount of from about 2 to about 200 grams per ton of total feed. For beef cattle, for example, a range of about 12 to 3000 mg/head/day is suitable. For enhancing milk production in lactating ruminants, oral administration of a daily amount of from about 0.04 to about 16 mg/kg of body weight (or about 25 to about 5000 mg/ruminant/day) is suggested.

The following examples are provided to illustrate this invention. To simplify discussion, "N ^{van}" is used to indicate the nitrogen on vancosamine and "N ^{leu}" is used to indicate the nitrogen in the leucine group. Reactions were followed by analytical high performance liquid chromatography (HPLC) using a Water's Bondapak C_{18} column with a gradient solvent system of CH_3CN and 0.5% triethylamine (pH 3) buffer and detecting with UV at 254 nm.

Examples 1-2

Preparation of N^{van}-(n-Decylidenyl)vancomycin - (Compound 100) and N^{van}-(n-Decyl)vancomycin - (Compound 2)

Vancomycin free base (5 g, 3.58 mmoles) was dissolved in dimethylformamide (DMF, 75 ml). n-Decyl aldehyde (0.7 ml, 3.72 mmoles) was added. The reaction mixture was stirred for 2 hours in a 70°C. oil bath to give N^{van}-(n-decylidenyl)-vancomycin (Compound 100).

Sodium cyanoborohydride (275 mg. 4.4 mmoles) was added to the solution containing Compound 100. The reaction mixture was stirred for another 2 hours in the oil bath and then was cooled to room temperature and transferred to a Virtis jar. Celite was added until a thick paste formed. The paste was evaporated under vacuum overnight. The powdery residue obtained was stirred with methanol and filtered three times. The methanol filtrates were combined and evaporated to dryness under vacuum. The residue obtained was triturated with diethyl ether. The insoluble residue was dissolved in methanol and filtered, and the filtrate was evaporated to dryness under vacuum.

This product was purified by reversed-phase high performance liquid chromatography (HPLC), using a Water's Prep Pak/500 column, eluting with an aceto-nitrile-water gradient system and detecting with UV at 280 nm, to give 793.5 mg of N^{van}-(n-decyl)vancomycin (Compound 2). The identity of the product was confirmed by fast-atom-bombardment mass spectrometry (FABMS).

Examples 3-30

The procedure described Examples 1-2 (with the appropriate starting aldehyde) was used to prepare mono-N^{van}-, mono-N^{leu}-and di-N ^{van}, N^{leu} derivatives. In general, the smaller the group to be added, the more complex the crude product and the more difficult the isolation. Generally, the major product is the N^{van}derivative. When A51568A is the

The compounds of this invention have also shown in vivo antimicrobial activity against experimental bacterial infections. When two doses of t st compound were administered to mice in experimental infections, the activity observed was measured as an ED_{50} value [effective dose in mg/kg to protect 50% of the test aminals: see Warren Wick, et al., J. Bacteriol. 81, 233-235 (1961)]. ED_{50} values observed are given in Table VIII.

Table VIII: ED_{50} Values for Formula I Compounds[a]

Organism	ED_{50} (mg/kg/2) Compound Numbers[b]					
	1	2	3	5	7	8
Staphylococcus aureus	>5	1.8	>5	2.9	3.4	>5
Streptococcus pyogenes	0.31	1.6	4.6	0.56	0.98	3.7
Streptococcus pneumoniae	0.42	0.51	3..6	0.81	0.44	3.1

[a]Administered subcutaneously

[b]Compound numbers from Table I

Pharmaceutical formulations of formula (I) and their pharmaceutically acceptable salts are also part of this invention. Thus, a formula (I) compound, preferably as a pharmaceutically acceptable salt, can be formulated for oral or parenteral administration for the therapeutic or prophylactic treatment of bacterial infections. For example, the compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers and the like. The compositions comprising a formula (I) compound will contain from about 0.1 to about 90% by weight of the active compound, and more generally from about 10 to about 30%. The compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose sodium, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid. Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica. Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. It may be desirable to add a coloring agent to make the dosage form more esthetic in appearance or to help identify the product.

For intravenous (IV) use, a water soluble form of the antibiotic can be dissolved in one of the commonly used intravenous fluids and administered by infusion. Such fluids as, for example, physiological saline, Ringer's solution or 5% dextrose solution can be used.

For intramuscular preparations, a sterile formulation of a suitable soluble salt form of the compound, for example the hydrochloride salt, can be dissolved and administered in a pharmaceutical diluent such as Water-for-Injection, physiological saline or 5% glucose solution. A suitable insoluble form of the compound may be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, e.g. an ester of a long chain fatty acid such as ethyl oleate.

For oral use, a sterile formulation of a suitable salt form of the antibiotic, for example the hydrochloride salt, formulated in a diluent such as distilled or deionized water, is particularly useful.

Table VII : In Vitro Activity of Formula 1 and 2 Compounds cont'd.

Organism	MIC (mcg/ml) Compound Number[a]									
	12	13	15	17	19	20	22	24	26	124
Staphylococcus aureus NRRL B313	0.5	0.5	0.5	1	0.5	1	2	1	0.25	0.5
Staphylococcus aureus V41	1	1	1	1	1	1	2	1	0.25	0.5
Staphylococcus aureus X400	1	1	1	1	1	1	2	2	0.25	0.5
Staphylococcus aureus S13E	1	0.5	1	1	1	1	2	1	0.25	0.5
Staphylococcus epidermidis EPI1	2	2	2	4	2	4	4	2	0.5	1
Staphylococcus epidermidis 222	1	1	1	2	1	1	4	2	0.25	0.5
Streptococcus pyogenes C203	0.5	0.5	0.5	1	0.5	0.5	2	1	0.25	0.25
Streptococcus pneumoniae Park 1	0.5	0.125	0.125	0.5	0.5	0.5	1	1	0.25	0.5
Streptococcus faecium ATCC 9790	1	1	1	2	1	1	2	2	0.5	0.5
Streptococcus sp. group D 2041	1	1	2	4	2	1	8	4	0.5	0.5
Haemophilus influenzae C.L.	>128	128	128	128	>128	128	>128	<128	128	>64
Haemophilus influenzae 76	128	128	128	128	128	128	128	128	128	>64
Escherichia coli N10	>128	>128	>128	>128	>128	>128	>128	>128	>128	>64
Escherichia coli EC14	>128	>128	>128	>128	>128	>128	>128	>128	>128	>64
Escherichia coli TEM	>128	>128	>128	>128	>128	>128	>128	>128	>128	>64
Klebsiella pneumoniae X26	>128	>128	>128	>128	>128	>128	>128	>128	>128	>64
Klebsiella pneumoniae X68	>128	>128	>128	>128	>128	>128	>128	>128	>128	>64
Klebsiella pneumoniae KAE	>128	>128	>128	>128	>128	>128	>128	>128	>128	>64

[a]Compound Numbers from Tables I-V

Table VII : In Vitro Activity of Formula 1 and 2 Compounds

Organism	MIC (mcg/ml) Compound Number[a]									
	1	2	3	4	5	6	7	8	9	10
Staphylococcus aureus NRRL B313	0.25	0.125	0.5	2	0.25	1	0.25	0.5	1	0.25
Staphylococcus aureus V41	0.25	0.25	0.5	4	0.25	1	0.25	0.5	1	0.5
Staphylococcus aureus X400	0.25	0.25	0.5	4	0.25	1	0.25	1	1	0.5
Staphylococcus aureus S13E	0.25	0.25	0.5	4	0.25	2	0.25	1	1	0.5
Staphylococcus epidermidis EPI1	0.5	0.25	2	16	0.5	4	1	2	4	2
Staphylococcus epidermidis 222	0.125	0.25	1	4	0.25	2	0.5	1	2	1
Streptococcus pyogenes C203	0.125	0.06	0.5	2	0.125	1	0.125	0.5	0.5	0.5
Streptococcus pneumoniae Park 1	0.25	0.125	0.5	4	0.25	2	0.125	1	1	0.125
Streptococcus faecium ATCC 9790	0.25	0.25	0.5	4	0.25	1	0.25	1	1	0.5
Streptococcus sp. group D 2041	0.125	0.25	1	4	0.5	2	0.5	2	2	1
Haemophilus influenzae C.L.	>128	128	128	>128	64	>128	32	128	>128	128
Haemophilus influenzae 76	>128	128	>128	>128	64	>128	32	128	>128	128
Escherichia coli N10	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Escherichia coli EC14	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Escherichia coli TEM	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Klebsiella pneumoniae X26	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Klebsiella pneumoniae X68	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Klebsiella pneumoniae KAE	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128

Illustrative formula 2 compounds of this invention are listed in Tables V and VI.

Table V: Illustrative Formula 2b Compounds

Compound No.	R_{2a}	R_{3a}
124	Me	n-decyl
125	H	n-decyl
126	Me	n-hexadecyl
127	Me	isooctyl
128	Me	n-butyl
129	Me	benzyl
130	Me	5-hydroxypentyl
131	Me	3-(methylthio)-n-propyl
132	Me	3-phenyl-n-(prop-2-enyl)
133	H	(pyrid-3-yl)methyl
134	Me	benzyl

Table VI: Illustrative Formula 2a Compounds

Compound No.	R	R_{3a}-R_{4a} Group
135	Me	n-decylidenyl
136	H	n-decylidenyl
137	Me	n-hexadecylidenyl
138	Me	isooctylidenyl
139	Me	n-butylidenyl
140	Me	benzylidenyl
141	Me	5-hydroxy-n-pentylidenyl
142	Me	3-(methylthio)-n-propylidenyl
143	Me	3-phenyl-n-(prop-2-enylidenyl)
144	H	(pyrid-3-yl)methylidenyl
145	Me	benzylidenyl

The formula (I) compounds inhibit the growth of a broad spectrum of pathogenic bacteria, especially Gram-positive bacteria. Table VII summarizes the minimal inhibitory concentrations (MIC's) at which the compounds inhibit certain organisms, as determined by standard agar-dilution assays.

Table IV: Illustrative Formula la Compounds wherein R_3 and R_4 = Alkylidenyl or Alkenylidenyl[a]

Compound No.	R	R_3-R_4 Group
99	Me	n-dodecylidenyl
100	Me	n-decylidenyl
101	Me	n-nonylidenyl
102	Me	n-octylidenyl
103	Me	n-heptylidenyl
104	Me	n-hexylidenyl
105	Me	n-pentylidenyl
106	Me	n-butylidenyl
107	Me	n-propylidenyl
108	Me	ethylidenyl
109	H	n-decylidenyl
110	Me	isopentylidenyl
111	Me	5-hydroxy-n-pentylidenyl
112	Me	6-bromo-n-hexylidenyl
113	Me	3-ethoxy-n-propylidenyl
114	Me	benzylidenyl
115	Me	3-phenyl-n-(prop-2-enylidenyl)
116	Me	3-phenyl-n-propylidenyl
117	Me	(pyrid-4-yl)methylidenyl
118	Me	(2-amino-thiazol-4-yl)ethylidenyl
119	Me	phenethylidenyl
120	Me	(indol-3-yl)methylidenyl
121	Me	(adamant-1-yl)methylidenyl
122	Me	n-undecylidenyl
123	Me	3-(methylthio)-n-propylidenyl

[a] In these compounds, n = 1 and R_2 = H

Table III: Illustrative Formula 1a Compounds wherein R_1-R_2 and R_3-R_4 = Alkylidenyl or Alkenylidenyl[a]

Cmpd. No.	R	R_1-R_2 Group	R_3-R_4 Group
79	Me	n-decylidenyl	n-decylidenyl
80	Me	n-nonylidenyl	n-nonylidenyl
81	Me	n-octylidenyl	n-octylidenyl
82	Me	n-heptylidenyl	n-heptylidenyl
83	Me	n-butylidenyl	n-butylidenyl
84	Me	n-propylidenyl	n-propylidenyl
85	Me	ethylidenyl	ethylidenyl
86	H	n-decylidenyl	n-decylidenyl
87	Me	isopropylidenyl	isopropylidenyl
88	Me	5-hydroxy-n-pentylidenyl	5-hydroxy-n-pentylidenyl
89	Me	6-bromo-n-hexylidenyl	6-bromo-n-hexylidenyl
90	Me	3-ethoxy-n-propylidenyl	3-ethoxy-n-propylidenyl
91	Me	benzylidenyl	benzylidenyl
92	Me	3-phenyl-n-(prop-2-enylidenyl)	3-phenyl-n-(prop-2-enylidenyl)
93	Me	3-phenyl-n-propylidenyl	3-phenyl-n-propylidenyl
94	Me	(pyrid-4-yl)-methylidenyl	(pyrid-4-yl)-methylidenyl
95	Me	(2-aminothiazol-4-yl)ethylidenyl	(2-aminothiazol-4-yl)ethylidenyl
96	Me	phenethylidenyl	phenethylidenyl
97	Me	(indol-3-yl)-methylidenyl	(indol-3-yl)-methylidenyl
98	Me	(adamant-1-yl)-methylidenyl	(adamant-1-yl)-methylidenyl

[a]In these compounds, n = 1

Table II cont'd.

Compound No.	R	R_1-R_2 Group
64	H	n-decylidenyl
65	Me	isopropylidenyl
66	Me	5-hydroxy-n-pentylidenyl
67	Me	6-bromo-n-hexylidenyl
68	Me	3-ethoxy-n-propylidenyl
69	Me	benzylidenyl
70	Me	3-phenyl-n-(prop-2-enylidenyl)
71	Me	3-phenyl-n-propylidenyl
72	Me	(pyrid-4-yl)methylidenyl
73	Me	(2-amino-thiazol-4-yl)ethylidenyl
74	Me	phenethylidenyl
75	Me	(indol-3-yl)methylidenyl
76	Me	(adamant-1-yl)methylidenyl
77	Me	3-(methylthio)-n-propylidenyl
78	Me	n-undecylidenyl

[a]In these compounds, n = 1 and R_3 and R_4 = H

Table I cont'd.

Compound No.	R	R_2	R_3
41	Me	benzyl	benzyl
42	H	H	benzyl
43	Me	H	3-phenyl-n-(prop-2-enyl)
44	Me	3-phenyl-n-(prop-2-enyl)	H
45	Me	H	3-phenyl-n-propyl
46	Me	H	(pyrid-3-yl)methyl
47	Me	(pyrid-2-yl)methyl	H
48	Me	H	(2-amino-thiazol-4-yl)ethyl
49	H	H	phenethyl
50	Me	H	(indol-3-yl)methyl
51	Me	H	(adamant-1-yl)methyl
52	Me	H	n-undecyl
53	Me	H	3-(methylthio)-n-propyl
54	Me	3-(methylthio)-n-propyl	H

[a]In these compounds, n = 1 and R_4 = H

Table II: Illustrative Formula Ia Compounds wherein R_1-R_2 = Alkylidenyl or Alkenylidenyl[a]

Compound No.	R	R_1-R_2 Group
55	Me	n-decylidenyl
56	Me	n-nonylidenyl
57	Me	n-octylidenyl
58	Me	n-heptylidenyl
59	Me	n-hexylidenyl
60	Me	n-pentylidenyl
61	Me	n-butylidenyl
62	Me	n-propylidenyl
63	Me	ethylidenyl

Table I: Illustrative Formula 1b Compounds[a]

Compound No.	R	R_2	R_3
1	Me	H	n-dodecyl
2	Me	H	n-decyl
3	Me	n-decyl	H
4	Me	n-decyl	n-decyl
5	Me	H	n-nonyl
6	Me	n-nonyl	n-nonyl
7	Me	H	n-octyl
8	Me	n-octyl	H
9	Me	n-octyl	n-octyl
10	Me	H	n-heptyl
11	Me	n-heptyl	H
12	Me	n-heptyl	n-heptyl
13	Me	H	n-hexyl
14	Me	n-hexyl	H
15	Me	H	n-pentyl
16	Me	n-pentyl	H
17	Me	H	n-butyl
18	Me	n-butyl	H
19	Me	n-butyl	n-butyl
20	Me	H	n-propyl
21	Me	n-propyl	H
22	Me	n-propyl	n-propyl
23	Me	Et	H
24	Me	Et	Et
25	H	n-decyl	H
26	H	H	n-decyl
27	H	isooctyl	H
28	Me	Me	Me
29	Me	isopropyl	isopropyl
30	Me	H	isopropyl
31	Me	H	5-hydroxy-n-pentyl
32	Me	5-hydroxy-n-pentyl	H
33	Me	"	5-hydroxy-n-pentyl
34	Me	H	6-bromo-n-hexyl
35	Me	6-bromo-n-hexyl	H
36	Me	H	3-ethoxy-n-propyl
37	Me	3-ethoxy-n-propyl	H
38	Me	3-ethoxy-n-propyl	3-ethoxy-n-propyl
39	Me	H	benzyl
40	Me	benzyl	H

aldehyde or ketone in a polar aprotic solvent until th 2a compound is formed. A preferred temperature range for this process is from about 25° to about 70°C., and a preferred time is from about 2 to about 18 hours.

In yet another aspect, this invention provides a process for preparing a formula 2b compound which comprises reacting the corresponding formula 2a compound with a reducing agent to reduce the $R_6R_7C=N$-double bond in the formula 2a compound. A preferred reducing agent for this process is a borohydride such as, for example, sodium cyanoborohydride.

When preparing those formula 1b and 2b compounds wherein the R_2, R_3, or R_{3a} group contains a -C=C-group, the reducing agent used should be one which selectively reduces the $R_6R_7C=N$-group only. Sodium borohydride is an example of such a selective reducing agent.

The compounds of this invention are useful antibacterial agents. The formula 1b and 2b compounds are preferred for this purpose.

The formula 1b compounds wherein R_2 is hydrogen and R_3 is an R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl) group are especially useful. Within this group, those compounds wherein the R_3 moiety contains from eight to twelve carbon atoms are particularly beneficial.

The formula 1b compounds wherein R is methyl, R_2 is hydrogen and R_3 is an R_5-(C_1-C_6-alkyl or R_5-(C_2-C_6-alkenyl) group are more readily and inexpensively prepared since the starting mat rial, vancomycin, is a commercial product.

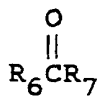
Another useful group of formula 1b compounds are those wherein R_3 is hydrogen and R_2 is an R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl) group. Preferred compounds within this group are those wherein th R_3 moiety contains from five to fourteen carbon atoms. Economically preferably compounds within this group are those wherein R is methyl (the compounds prepared from vancomycin).

Yet another group of formula 1b compounds are those wherein R_2 and R_3 are both R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl) groups. Again, the most preferred compounds of this subgroup are those wherein R is methyl.

Illustrative compounds of this invention are listed in Tables I-IV.

Compounds	Definition
1a	1 compounds wherein R_1 and R_2 or R_3 and R_4 together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group
1b	1 compounds wherein R_2 or R_3 is R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl)
2a	2 compounds wherein R_{3a} and R_{4a} together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group
2b	2 compounds wherein R_{3a} is R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl)

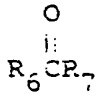
In one aspect, this invention provides a process for preparing a formula 1a compound which comprises reacting vancomycin, A51568A or A51568B with the corresponding



aldehyde or ketone wherein R_6 and R_7 are as defined, supra, preferably, in a polar aprotic solvent until 1a compound is formed. A preferred temperature range for this process is from about 25° to about 70°C, and a preferred time is from about 3 to about 18 hours.

In a second aspect, this invention provides a process for preparing a formula 1b compound which comprises reacting the corresponding formula 1a compound with a reducing agent to reduce the R_6R_7C=N-double bond(s) in the 1a compound. A preferred reducing agent for this process is a borohydride such as, for example, sodium cyanoborohydride.

In another aspect, this invention provides a process for preparing a formula 2a compound which comprises reacting M43A or M43D with the corresponding



The reduction of the Schiff's base thus formed can be effected using a chemical reducing agent such as a metal borohydride, for example sodium cyanoborohydride. Once again an aprotic solvent such as dimethylformamide is preferred and the reduction can be effected using temperatures in the range from 25 to 100°C, preferably about 70°C.

It will be appreciated that the sugar groups in the above formulae have the same configuration as do those in vancomycin, i.e., α-O-vancosaminyl-β-O-glucosyl.

Each R_6 and R_7 group may have from 1 to 15 carbon atoms, and preferably the sum of the carbon atoms in R_6 and R_7 is no greater than 15. Those compounds wherein either R_1 and R_2 or R_3 and R_4 together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group are known as Schiff bases.

The terms "C_1-C_5-alkyl", "C_1-C_6-alkyl" and "C_1-C_{10}-alkyl" refer to a saturated, straight-or branched-chain alkyl group containing the specified number of carbon atoms. The terms "C_2-C_5-alkenyl", "C_2-C_6-alkenyl" and "C_2-C_{10}-alkenyl" refer to an unsaturated straight or branched-chain alkenyl group containing the specified number of carbon atoms. Those compounds wherein R_2 or R_3 is R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl), referred to herein as "reduced Schiff bases", are prepared by reduction of the corresponding compounds wherein either R_1 and R_2 or R_3 and R_4 represent an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group.

Methoxy, ethoxy and tert-butoxy are typical C_1-C_6-alkoxy groups. Methylthio, n-propylthio and isopentylthio are typical C_1-C_6-alkylthio groups. Halo substituents are selected from the group consisting of chloro, bromo, fluoro and iodo. Cyclopropyl, cycloheptyl and cyclohexadienyl are examples of C_3-C_{10}-cycloalkyl and C_5-C_{12}-cycloalkenyl groups.

The formula 1 compounds can be prepared from the antibiotics vancomycin, A51568A and A51568B. The formula 2 compounds can be prepared from the antibiotics M43A and M43D.

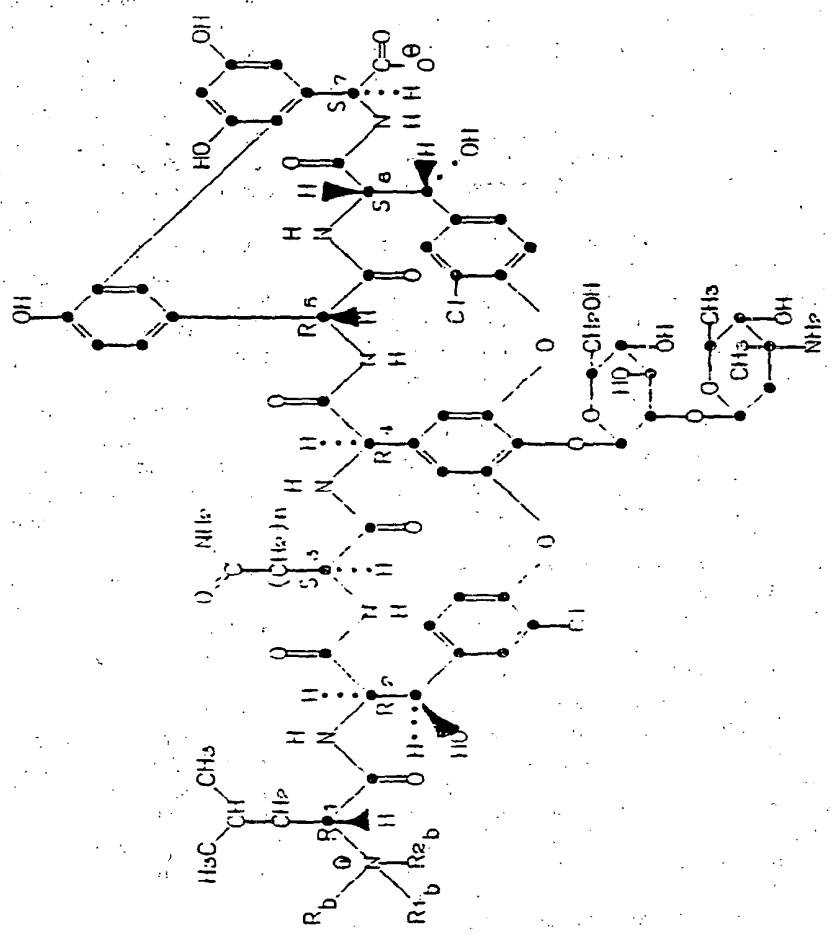
The compounds of the invention are shown as zwitterions. Those in the art will recognize, however, that each as a carboxyl group, one or two amino groups and three phenolic groups which can react to form various salts. All such forms of the compounds are part of this invention. The salts are useful, for example, for separating and purifying th antibiotics. In addition, the salts have an improved solubility in water.

The salts are prepared using standard procedures for salt preparation. For example, the zwitterion can be neutralized with an appropriate acid to form an acid addition salt.

The acid addition salts are particularly useful. Representative suitable salts include those salts formed by standard reactions with both organic and inorganic acids such as, for example, sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, cholic, pamoic, mucic, D-glutamic, d-camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

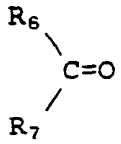
Pharmaceutically acceptable acid addition salts are an especially preferred group of salts of this invention.

This invention further relates to processes for preparing the compounds of the invention from the glycopeptide antibiotics vancomycin, A51568A, A51568B, M43A and M43D. For convenience in discussing the processes of this invention, the following subgroups are designated:



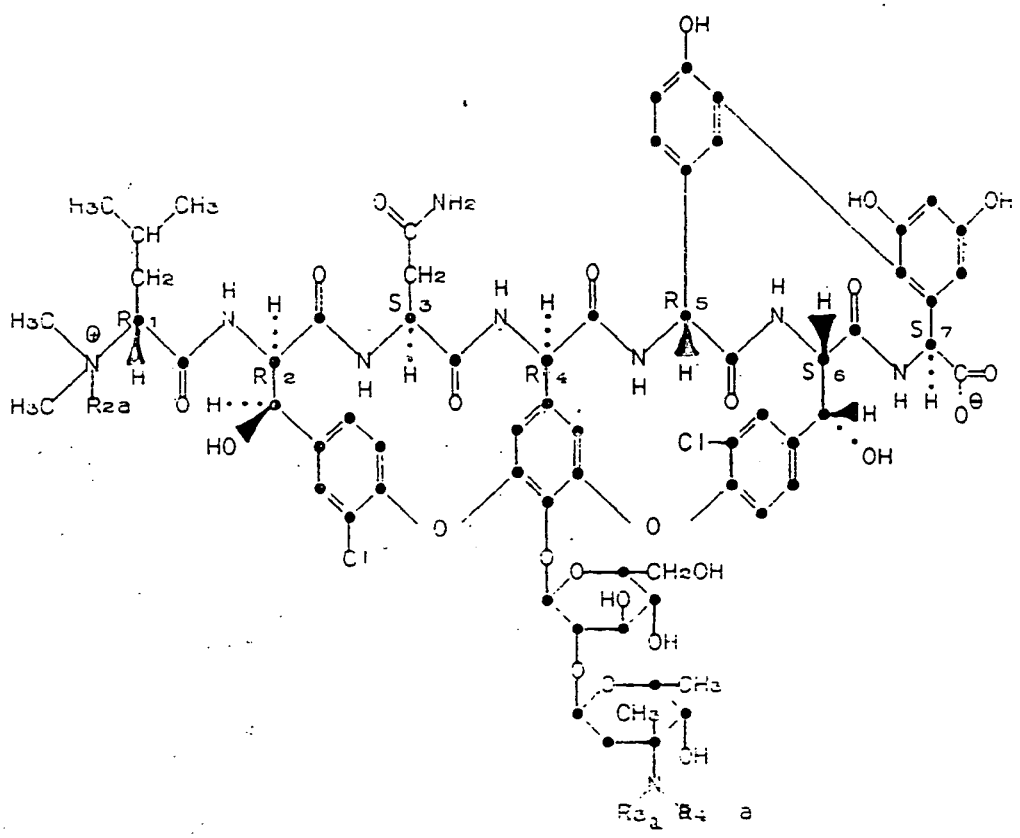
Compound	R_b	R_{1b}	R_{2b}	n
Vancomycin	CH_3	H	H	1
M43A	CH_3	CH_3	CH_3	1
M43D	CH_3	CH_3	H	1
A51568A	H	H	H	1
A51568B	H	H	H	2

with a ketone or aldehyde of formula:



so as to form alkylidene or alkenylidene derivatives of the invention, optionally followed by reduction so as to form alkyl or alkenyl derivatives.

The reaction with the R'R'CO compound is preferably carried out at temperatures between 25 and 100°C, preferably from 25 to 70°C, utilising a polar aprotic solvent such as dimethylformamide.



2

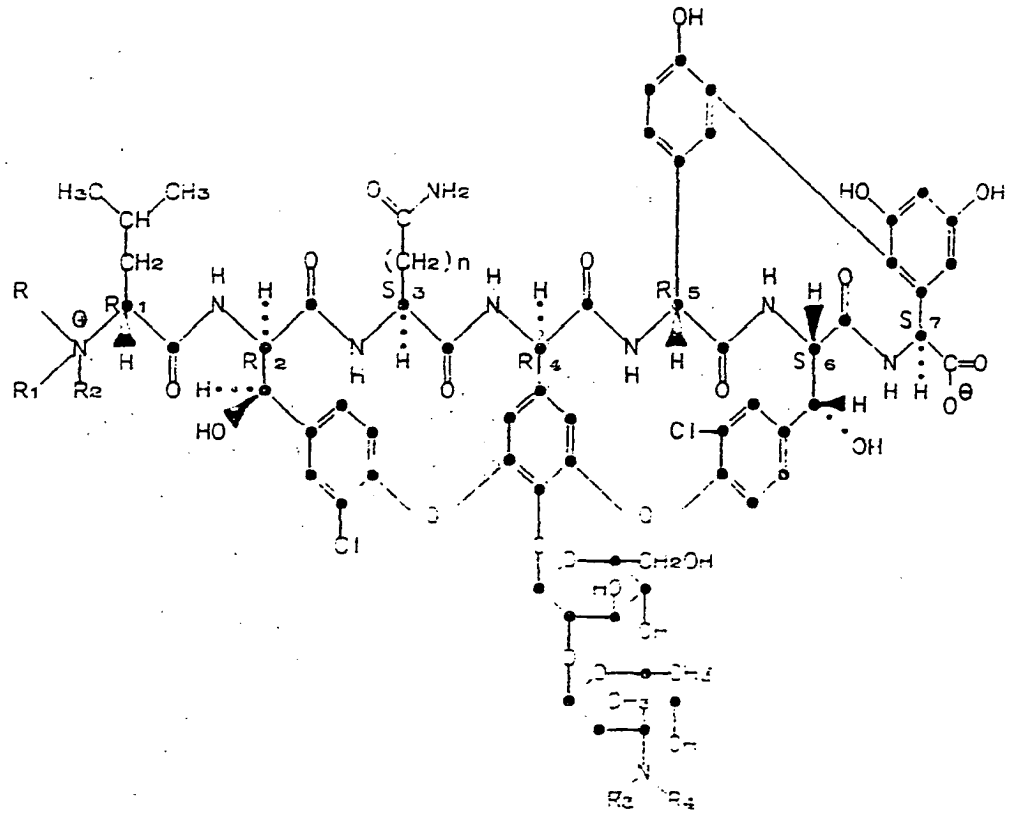
wherein R_{2a} is hydrogen or methyl;

R_{3a} is R_5-(C_1-C_6-alkyl) or R_5-(C_2-C_6-alkenyl);

R_{4a} is hydrogen; or

R_{3a} and R_{4a} together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group and salts of these compounds.

The compounds of the invention can be prepared by reacting vancomycin, antibiotic A51568 factor A, A51568 factor B, M43A or M43D, (see the following structural formula)



1

wherein R is hydrogen or methyl;

R_1 is hydrogen;

R_2 and R_3, independently, are hydrogen, R_5-(C_1-C_6)-alkyl or R_5-(C_2-C_6-alkenyl); and

R_4 is hydrogen; or

R_1 and R_2 or R_3 and R_4 together form an R_5-(C_1-C_6-alkylidenyl) or R_5-(C_2-C_6-alkenylidenyl) group;

R_5 is C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_3-C_{10}-cycloalkyl, C_5-C_{12}-cycloalkenyl, phenyl, napththyl, indenyl, tetralinyl, decalinyl, adamantyl, a monocyclic heterocyclic ring system comprising 3 to 8 atoms in the ring or a bicyclic heterocyclic ring system comprising 6 to 11 atoms, provided that at least one atom of the ring system is carbon and at least one atom of the ring system is a heteroatom selected from O, N and S, and wherein R_5 may be substituted with one or more hydroxy, C_1-C_6-alkoxy, C_1-C_6-alkylthio, halo or amino groups; and

n = 1 or 2;

provided that: 1) at least one of R_2 and R_3 must be other than hydrogen; and 2) when n is 2, R must be hydrogen;

and the salts of these compounds.

Compounds in which R_2 is a group of formula R_4R_5CH-and R_3 is hydrogen are preferred.

This invention also relates to novel glycopeptide derivatives of formula 2:

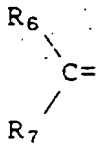
wherein R and R_1 are independently hydrogen or methyl;

R_2 and R_3, independently, are hydrogen, or a group of formula: R_6R_7CH-, where R_6 and R_7 are independently R_5, R_5-(C_1-C_5) alkyl or R_5-(C_2-C_5) alkenyl; wherein R_5 is hydrogen, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_1-C_4 alkoxy, C_3-C_{10}-cycloalkyl, C_5-C_{12}-cycloalkenyl, phenyl, napththyl, indenyl, tetralinyl, decalinyl, adamantyl, a monocyclic heterocyclic ring system comprising 3 to 8 atoms in the ring or a bicyclic heterocyclic ring system comprising 6 to 11 atoms, provided that at least one atom of the ring system is carbon and at least one atom of the ring system is a heteroatom selected from O, N and S, and wherein R_5 may be substituted with one or more hydroxy, nitro, C_1-C_{10}-alkoxy, C_1-C_{10} alkyl, phenyl, C_1-C_6-alkylthio, nitrole, halo, C_2-C_4 acylamino, amino, C_1-C_4 dialkylamino groups;

and

R_4 is hydrogen; or

R_1 and R_2 and/or R_3 and R_4 together form a group of the formula



wherein R_6 and R_7 are R_5, R_5-(C_1-C_5 alkyl) or R_5-(C_2-C_5-alkenyl),

and n is 1 or 2;

provided that: 1) at least one of R_2 and R_3 must be other than hydrogen; 2) when n is 2, R must be hydrogen; 3) when R is methyl and R_3 is hydrogen, R_2 cannot be methyl and 4) when R and R_1 are both methyl, then R_2 is hydrogen or methyl and n is 1;

and salts of these compounds.

Thus, in one aspect of the invention there are provided compounds of formula 1:

NOVEL GLYCOPEPTIDE DERIVATIVES

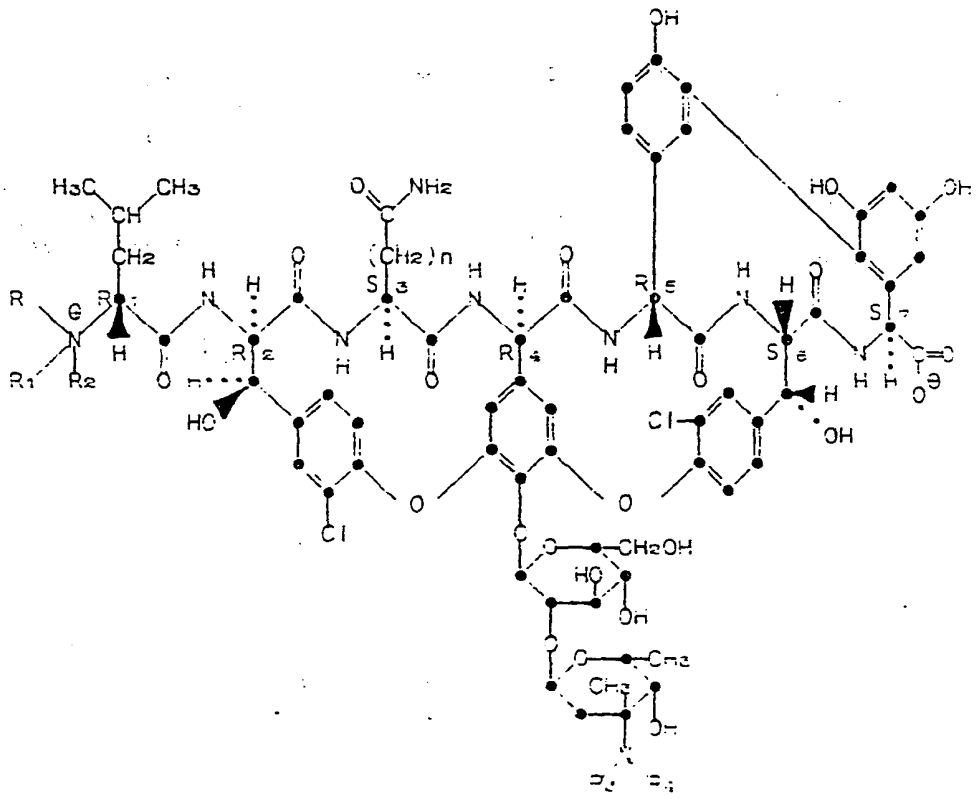
This invention relates to new glycopeptide derivatives having useful antibacterial activity, and to methods for preparing these compounds.

New, improved antibiotics are continually in demand, particularly for the treatment of human diseases. Increased potency, expanded spectrum of bacterial inhibition, increased in vivo efficacy, and improved pharmaceutical properties (such as greater oral absorption, higher blood or tissue concentrations, longer in vivo half life, and more advantageous rate or route of excretion and rate or pattern of metabolism) are some of the goals for improved antibiotics.

In the search for new antibiotics, structural modification of known antibiotics is attempted whenever possible. Many antibiotics, including the glycopeptides, however, have such complex structures that even small changes are difficult to make. Furthermore, it is difficult to predict the effect these changes will make in the desired activity. Processes for modifying known antibiotics and the new active derivatives made by such processes continue, therefore, to be of great importance.

The compounds of the invention are new members of the glycopeptide group of antibiotics. The compounds can be prepared from the known glycopeptides vancomycin (see, for example, U.S. Patent 3,067,099), antibiotic A51568 factor A (see U.S. Patent 4,495,179) and A51568 factor B (see U.S. Patent 4,558,008; antibiotic M43A (see U.S. Patent No. 4,548,925), and antibiotic M43D (see U.S. Patent No. 4,547,488).

According to the present invention there are provided compounds of formula (I):



I

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 201 251**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **86303158.9**

(22) Date of filing: **25.04.86**

(51) Int. Cl.⁴: **C07K 9/00** , A61K 37/02

(30) Priority: **25.04.85 US 726731**

(43) Date of publication of application:
17.12.86 Bulletin 86/46

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: **ELI LILLY AND COMPANY**
Lilly Corporate Center
Indianapolis Indiana 46285(US)

(72) Inventor: **Nagarajan, Ramakrishnan**
5 West 79th Street
Indianapolis Indiana 46260(US)
Inventor: **Schabel, Amelia Apolinaria**
4455 Broadway
Indianapolis Indiana 46205(US)

(74) Representative: **Tapping, Kenneth George et al**
Erl Wood Manor
Windlesham Surrey, GU20 6PH(GB)

(54) **Novel glycopeptide derivatives.**

(57) Novel glycopeptide antibiotics can be prepared from the glycopeptide antibiotics vancomycin, A51568A, A51568B, M43A and M43D by reaction with a ketone or aldehyde followed, if appropriate, by reduction.

EP 0 201 251 A2